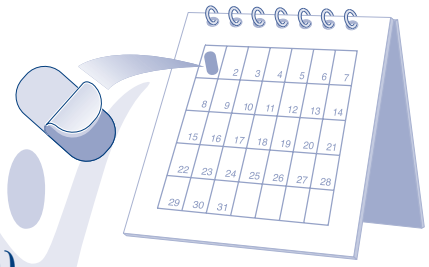
Bonviva® 150 mg

Roche

film-coated tablets

Ibandronic acid

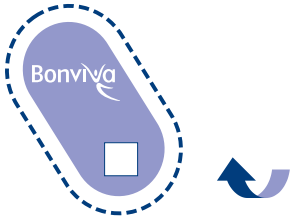
PLANNING WHEN TO TAKE BONVIVA



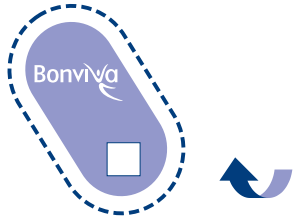
The dose of Bonviva is one tablet once a month.
Choose one day of the month that will be easy
to remember:
– either the same date (such as the 1st of each month)
– or the same day (such as the first Sunday of each month).
Use the peel-off stickers below to mark the dates on your calendar.
Once you've taken your tablet, put a tick in the box on the sticker.

PEEL-OFF STICKERS FOR YOUR PERSONAL CALENDAR

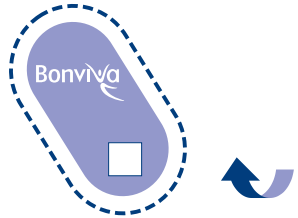
Monthly tablet



Monthly tablet



Monthly tablet



It's important to keep taking Bonviva every month. Remember to contact your doctor when you need a new prescription.

In this leaflet:

Bonviva® 150 mg

film-coated tablets

Ibandronic acid

Bisphosphonates – Drugs for treatment of bone diseases (M05)

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Bonviva is a nitrogen-containing bisphosphonate.

1.2 Type of Dosage Form

Film-coated tablets.

1.3 Route of Administration

Oral.

1.4 Qualitative and Quantitative Composition

Active ingredient: ibandronic acid, monosodium salt, monohydrate.

One 150 mg film-coated tablet contains 168.75 mg of ibandronic acid, monosodium salt, monohydrate equivalent to 150 mg of ibandronic acid.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Treatment of postmenopausal osteoporosis

Bonviva 150 mg is indicated for the treatment of postmenopausal osteoporosis, to reduce the risk of fractures.

Osteoporosis may be confirmed by the finding of low bone mass (T-score <-2.0 SD) and the presence or history of osteoporotic fracture, or a low bone mass (T-score < -2.5 SD) in the absence of documented pre-existing osteoporotic fracture.

2.2 Dosage and Administration

The recommended dose of Bonviva for treatment is one 150 mg film-coated tablet once a month. The tablet should preferably be taken on the same date each month.

Bonviva should be taken 60 minutes before the first food or drink (other than water) of the day (see section 2.4.3 Interactions with other Medicinal Products and other Forms of Interaction, Drug-Food Interactions) or any other oral medication or supplementation (including calcium):

– Tablets should be swallowed whole with a full glass of plain water (180 to 240 ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 60 minutes after taking Bonviva.

– Plain water is the only drink that should be taken with Bonviva. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
– Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.

Patients should receive supplemental calcium or vitamin D if dietary intake is inadequate.

In case a once-monthly dose is missed, patients should be instructed to take one Bonviva 150 mg tablet the morning after the tablet is remembered, unless the time to the next scheduled dose is within 7 days. Patients should then return to taking their dose once a month on their originally scheduled date.

If the next scheduled dose is within 7 days, patients should wait until their next dose and then continue taking one tablet once a month as originally scheduled. Patients should not take two 150 mg tablets within the same week.

2.2.1 Special Dosage Instructions

Patients with hepatic impairment

No dosage adjustment is necessary (see section 3.2.5 Pharmacokinetics in Special Populations).

Patients with renal impairment

No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is ≥30 ml/min.

Below 30 ml/min creatinine clearance, the decision to administer Bonviva should be based on an individual risk-benefit assessment (see section 3.2.5 Pharmacokinetics in Special Populations).

Elderly
No dosage adjustment is necessary.

Children
Safety and efficacy have not been established in patients less than 18 years old.

2.3 Contraindications

Bonviva is contraindicated in patients with known hypersensitivity to ibandronic acid or to any of the excipients. Bonviva is contraindicated in patients with uncorrected hypocalcemia. As with all bisphosphonates indicated in the

treatment of osteoporosis, pre-existing hypocalcemia needs to be corrected before initiating therapy with Bonviva. As with several bisphosphonates, Bonviva is contraindicated in patients with abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia (see section 2.4 Warnings and Precautions). Bonviva is contraindicated in patients who are unable to stand or sit upright for at least 60 minutes (see sections 2.2 Dosage and Administration and 2.4 Warnings and Precautions).

2.4 Warnings and Precautions

2.4.1 General

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Bonviva therapy. Adequate intake of calcium and vitamin D is important in all patients.

Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Bonviva is given to patients with active upper gastrointestinal problems (e.g. known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers).
Adverse experiences such as esophagitis, esophageal ulcers and esophageal erosions, in some cases severe and requiring hospitalization, rarely with bleeding or followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. The risk of severe esophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction and/or who continue to take oral

bisphosphonates after developing symptoms suggestive of esophageal irritation. Patients should pay particular attention and be able to comply with the dosing instructions (see section 2.2 Dosage and Administration).
Physicians should be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue Bonviva and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.
While no increased risk was observed in controlled clinical trials there have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications. Since NSAIDs and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant medication with Bonviva.

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis of the jaw include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, including angiogenesis inhibitors, radiotherapy, corticosteroids), and co-morbid disorders (e.g., anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally.
For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether

discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit-risk assessment.
Cases of osteonecrosis of other oro-facial sites including the external auditory canal have also been reported in patients treated with bisphosphonates including IBN. Risk factors are similar as for ONJ. Other risk factors may include repetitive minor trauma (e.g., habitual cotton bud use). The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

2.4.2 Ability to Drive and Use Machines

No studies on the effects of Bonviva on the ability to drive and use machines have been performed.

2.4.3 Interactions with other Medicinal Products and other Forms of Interaction

Drug-Food Interactions

Products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk and food, are likely to interfere with absorption of Bonviva which is consistent with findings in animal studies. Therefore, with such products, including food, intake must be delayed for 60 minutes following oral administration.

Drug-Drug Interactions

It is likely that calcium supplements, antacids and some oral medications containing multivalent cations (such as aluminium, magnesium, iron) are

likely to interfere with the absorption of Bonviva. Therefore, patients must wait 60 minutes after taking Bonviva before taking other oral medications. Pharmacokinetic interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (estrogen). No interaction was observed when co-administered with melphalan/prednisolone in patients with multiple myeloma. In healthy male volunteers and postmenopausal women, i.v. ranitidine caused an increase in ibandronic acid bioavailability of about 20 %, probably as a result of reduced gastric acidity. However, since this increase is within the normal range of the bioavailability of ibandronic acid, no dosage adjustment is required when Bonviva is administered with H_2-antagonists or other drugs which increase gastric pH.

In relation to disposition, no drug interactions of clinical significance are considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats. Furthermore, plasma protein binding is low at therapeutic concentrations and ibandronic acid is therefore unlikely to displace other drugs. Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation. The secretory pathway appears not to include known acidic or basic transport systems involved in the excretion of other drugs.
In a one-year study in postmenopausal women with osteoporosis (BM16549), the incidence of upper gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in patients taking Bonviva 2.5 mg daily or 150 mg once monthly.

Of over 1,500 patients enrolled in study BM16549 comparing monthly with daily dosing regimens of ibandronic acid, 14% of patients used histamine (H2) blockers or proton pump inhibitors. Among these patients, the incidence of upper gastrointestinal events in the patients treated with Bonviva 150 mg once monthly was similar to that in patients treated with Bonviva 2.5 mg daily.

2.5 Use in Special Populations

2.5.1 Pregnancy

Bonviva should not be used during pregnancy.

There was no evidence for a direct fetal toxic or teratogenic effect of ibandronic acid in daily orally treated rats and rabbits and there were no adverse effects on the development in F_1 offspring in rats. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those observed with bisphosphonates

as a class. They include a decreased number of implantation sites, interference with natural delivery (dystocia), and an increase in visceral variations (renal pelvis ureter syndrome). Specific studies for the monthly regimen have not been performed. There is no clinical experience with Bonviva in pregnant women.

2.5.2 Nursing Mothers

Bonviva should not be used during lactation.
In lactating rats treated with 0.08 mg/kg/day i.v. ibandronic acid, the highest concentration of ibandronic acid in breast milk was 8.1 ng/ml and was seen in the first 2 hours after i.v. administration. After 24 hours, the concentration in milk and plasma was similar, and corresponded to about 5 % of the concentration measured after 2 hours.
It is not known whether Bonviva is excreted in human milk.

2.5.3 Pediatric Use

See section 3.2.5 Pharmacokinetics in Special Populations, Children.

2.5.4 Geriatric Use

See section 3.2.5 Pharmacokinetics in Special Populations, Elderly.

2.5.5 Renal Impairment

See section 3.2.5 Pharmacokinetics in Special Populations, Patients with renal impairment.

2.5.6 Hepatic Impairment

See section 3.2.5 Pharmacokinetics in Special Populations, Patients with hepatic impairment.

2.6 Undesirable Effects

2.6.1 Clinical Trials

Treatment of postmenopausal osteoporosis

Once-monthly dosing

In a two-year study in postmenopausal women with osteoporosis (BM16549) the overall safety of Bonviva 150 mg once monthly and Bonviva 2.5 mg daily was similar. The overall proportion of patients who experienced an adverse drug reaction, i.e. adverse event with a possible or probable relationship to trial medication, was 22.7 % and 25.0 % for Bonviva 150 mg once monthly and 21.5 % and 22.5 % for Bonviva 2.5 mg daily after one and two years, respectively. The majority of adverse drug reactions were mild to moderate in intensity. Most cases did not lead to cessation of therapy.

Tables 1 and 2 list adverse drug reactions occurring in more than 1 % of patients treated with Bonviva 150 mg monthly or 2.5 mg daily in study BM16549 and in patients treated with Bonviva 2.5 mg daily in study MF4411. The tables show the adverse drug reactions in the two studies that occurred with a higher incidence than in patients treated with placebo in study MF4411. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Data at one year from study BM16549 are represented in Table 1 and cumulative data for the two years from study BM16549 are represented in Table 2.

Table 1: Common adverse drug reactions (>1/100, ≤ 1/10) in phase III osteoporosis studies that were considered by the investigator to be possibly or probably related to treatment - One-year data from study BM16549 and three-year data from placebo-controlled fracture study MF4411

	One-year data in study BM16549		Three-year data in study MF4411	
System Organ Class/ Adverse drug reaction	**Bonviva 150 mg once monthly (N=396) (%)**	**Bonviva 2.5 mg daily (N=395) (%)**	**Bonviva 2.5 mg daily (N=977) (%)**	**Placebo (N=975) (%)**
Gastrointestinal system				
Gastroesophageal reflux disease	0.5	1.0	0.4	0.1
Diarrhea	2.5	1.8	1.4	1.0

	One-year data in study BM16549		Three-year data in study MF4411	
System Organ Class/ Adverse drug reaction	**Bonviva 150 mg once monthly (N=396) (%)**	**Bonviva 2.5 mg daily (N=395) (%)**	**Bonviva 2.5 mg daily (N=977) (%)**	**Placebo (N=975) (%)**
Abdominal pain	3.5	2.8	2.1	2.9
Dyspepsia	3.3	5.8	4.3	2.9
Nausea	3.3	3.5	1.8	2.3
Flatulence	0.5	1.0	0.4	0.7
Nervous system				
Headache	0.8	1.5	0.8	0.6

	One-year data in study BM16549		Three-year data in study MF4411	
System Organ Class/ Adverse drug reaction	**Bonviva 150 mg once monthly (N=396) (%)**	**Bonviva 2.5 mg daily (N=395) (%)**	**Bonviva 2.5 mg daily (N=977) (%)**	**Placebo (N=975) (%)**
General disorders				
Influenza-like illness*	3.3	0.3	0.3	0.2
Fatigue	1.0	0.3	0.3	0.4
Musculoskeletal system				
Arthralgia	1.0	0.3	0.4	0.4
Myalgia	1.5	0.3	1.8	0.8

	One-year data in study BM16549		Three-year data in study MF4411	
System Organ Class/ Adverse drug reaction	**Bonviva 150 mg once monthly (N=396) (%)**	**Bonviva 2.5 mg daily (N=395) (%)**	**Bonviva 2.5 mg daily (N=977) (%)**	**Placebo (N=975) (%)**
Skin disorders				
Rash	0.8	1.0	1.2	0.7

MedDRA version 6.1

* Transient, influenza-like symptoms have been reported with Bonviva 150 mg once monthly, typically in association with the first dose. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures. Influenza-like illness includes events reported as acute phase reaction or symptoms including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, or bone pain.

Table 2: Cumulative common adverse drug reactions (>1/100, ≤ 1/10) in Phase III osteoporosis studies that were considered by the investigator to be possibly or probably related to treatment - Two-year data from study BM16549 and three-year data from placebo-controlled fracture study MF4411				
	Two-year cumulative data in study BM16549		Three-year data in study MF4411	
System Organ Class/ Adverse drug reaction	Bonviva 150 mg once monthly (N=396) (%)	Bonviva 2.5 mg daily (N=395) (%)	Bonviva 2.5 mg daily (N=977) (%)	Placebo (N=975) (%)
Gastrointestinal system				
Gastritis	1.0	0.3	0.7	0.5
Gastroesophageal reflux disease	0.8	1.0	0.5	0.1

Esophagitis	0	1.0	0.5	0.4
Diarrhea	2.5	2.0	1.4	1.0
Abdominal pain	4.0	3.0	2.1	2.9
Dyspepsia	4.0	6.3	4.0	2.7
Nausea	3.0	3.5	1.8	2.3
Nervous system				
Headache	0.8	1.5	0.8	0.6
General disorders				
Influenza-like illness*	3.3	0.3	0.3	0.2
Musculoskeletal system				
Muscle cramp	0.5	1.0	0.1	0.4

Musculoskeletal pain	1.0	0.5	0	0
Arthralgia	1.0	0.5	0.4	0.4
Myalgia	1.5	0.3	1.8	0.8
Musculoskeletal stiffness	1.0	0	0	0
Skin disorders				
Rash	0.8	1.0	1.2	0.7

MedDRA version 7.1

* Transient, influenza-like symptoms have been reported with Bonviva 150 mg once monthly, typically in association with the first dose. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures. Influenza-like illness includes events reported as acute phase reaction or symptoms including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, or bone pain.

Adverse drug reactions occurring at a frequency of less than or equal to 1 %
The following list provides information on adverse drug reactions (considered possibly or probably related to treatment by the investigator) reported in study MF4411 occurring more frequently with Bonviva 2.5 mg daily than with placebo and study BM16549 occurring more frequently with Bonviva 150 mg once monthly than with Bonviva 2.5 mg daily. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Uncommon (1/100 – 1/1,000)
Gastrointestinal Disorders: gastritis, esophagitis, including esophageal ulcerations or strictures, vomiting, dysphagia
Nervous System Disorders: dizziness
Musculoskeletal and Connective Tissue Disorders: back pain

Rare (1/1,000 – 1/10,000)
Gastrointestinal Disorders: duodenitis
Immune System Disorders: hypersensitivity reactions
Skin and Subcutaneous Tissue Disorders: angioedema, face edema, urticaria

Patients with a previous history of gastrointestinal disease including patients with peptic ulcer without recent bleeding or hospitalization, and patients with dyspepsia or reflux controlled by medication were included in the once-monthly treatment study. For these patients, there was no difference in the incidence of upper gastrointestinal adverse events with the 150 mg once-monthly regimen compared to the 2.5 mg daily regimen.

2.6.1.1 Laboratory Abnormalities

In the pivotal three-year study with Bonviva 2.5 mg daily (MF4411) there was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, impaired hematologic system, hypocalcemia or hypophosphatemia. Similarly, no differences were noted between the groups in study BM16549 after one and two years.

2.6.2 Post Marketing

Musculoskeletal and connective tissue disorders:
Osteonecrosis of the jaw and other oro-facial sites, including the external auditory canal has been reported very rarely in patients treated with ibandronic acid (see section 2.4 Warnings and Precautions).

Eye disorders:
Ocular inflammation events such as uveitis, episcleritis and scleritis have been reported with bisphosphonates, including ibandronic acid. In some cases, these events did not resolve until the bisphosphonate was discontinued.

Immune system disorders:
Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with ibandronic acid.
Allergic reactions including asthma exacerbation have been reported. Severe Cutaneous Adverse Reactions including Stevens-Johnson Syndrome, Erythema Multiforme, and Bullous Dermatitis, have been reported.

Injury, poisoning and procedural complications:
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, including ibandronate, however causality has not been established.

2.7 Overdose

No specific information is available on the treatment of overdosage with Bonviva. However, oral overdosage may result in upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer. Milk or antacids should be given to bind Bonviva. Owing to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

The pharmacodynamic action of ibandronic acid is inhibition of bone resorption. In vivo, ibandronic acid prevents experimentally induced bone destruction caused by cessation of gonadal function, retinoids, tumors or tumor extracts. In young (fast growing) rats, the endogenous bone resorption is also inhibited, leading to increased bone mass compared with untreated animals.
Animal models confirm that ibandronic acid is a highly potent inhibitor of osteoclastic activity. In growing rats, there was no evidence of impaired mineralization even at doses greater than 5,000 times the dose required for osteoporosis treatment.

The high potency and therapeutic margin of ibandronic acid allows for more flexible dosing regimens and intermittent treatment with long drug-free intervals at comparatively low doses.
Both daily and intermittent (with prolonged dose-free intervals) long-term administration in rats, dogs and monkeys were associated with formation of new bone of normal quality and/or increased mechanical strength even in doses in excess of any pharmacologically intended dose, including the toxic range. In humans, the efficacy of both daily and intermittent administration with a dose-free interval of 9-10 weeks of ibandronic acid was confirmed in a clinical trial (MF4411), in which Bonviva demonstrated anti-fracture efficacy.
Both daily and intermittent (with a drug-free interval of 9-10 weeks per quarter) oral doses of Bonviva in postmenopausal women produced biochemical changes

indicative of dose-dependent inhibition of bone resorption, including suppression of urinary biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked C- and N-telopeptides of type I collagen). Following treatment discontinuation, there is a reversion to the pathological pre-treatment rates of elevated bone resorption associated with postmenopausal osteoporosis.

The histological analysis of bone biopsies after two and three years of treatment of postmenopausal women showed bone of normal quality and no indication of a mineralization defect.

In a Phase I bioequivalence study conducted in 72 postmenopausal women receiving 150 mg orally every 28 days for a total of four doses, inhibition in serum CTX following the first dose was seen as early as 24 hours post-dose

(median inhibition 28%), with median maximal inhibition (69%) seen 6 days later. Following the third and fourth dose, the median maximum inhibition 6 days post-dose was 74% with reduction to a median inhibition of 56% seen 28 days following the fourth dose. With no further dosing, there is a loss of suppression of biochemical markers of bone resorption.

3.1.1 Mechanism of Action

Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act on bone tissue and specifically inhibit osteoclast activity. It does not interfere with osteoclast recruitment. The selective action of ibandronic acid on bone tissue is based on the high affinity of this compound for hydroxyapatite, which represents the mineral matrix of the bone. Ibandronic acid reduces bone resorption, with no direct effect on bone formation.

In postmenopausal women, it reduces the elevated rate of bone turnover towards premenopausal levels, leading to a progressive net gain in bone mass. Daily or intermittent administration of ibandronic acid results in reduced bone resorption as reflected in reduced levels of serum and urinary biochemical markers of bone turnover, increased bone mineral density (BMD) and a decreased incidence of fractures.

3.1.2 Clinical / Efficacy Studies

Treatment of postmenopausal osteoporosis

In the initial three-year, randomized, double-blind, placebo-controlled, fracture study (MF4411), a statistically significant and medically relevant decrease in the incidence of new radiographic morphometric and clinical vertebral fractures was demonstrated. Bonviva was evaluated at oral doses of 2.5 mg daily and

20 mg intermittently (20 mg every other day for 12 doses at the start of each 3-month cycle, followed by a 9-10 week drug-free interval). Bonviva was taken 60 minutes before the first food or drink of the day (post-dose fasting period). The study enrolled 2,946 women aged 55 to 80 years (2,928 were eligible for efficacy), who were at least 5 years postmenopausal, who had a lumbar spine BMD 2 to 5 SD below the premenopausal mean (T-score) in at least one vertebra [L1-L4], and who had one to four prevalent vertebral fractures. All patients received 500 mg calcium and 400 IU vitamin D daily.
Bonviva showed a statistically significant and medically relevant reduction in the incidence of new vertebral fracture with both regimens tested. The 2.5 mg daily regimen reduced the occurrence of new radiographic vertebral fractures by 62% over the three-year duration of the study. Clinical vertebral fractures were also reduced by 49%. The strong effect on vertebral fractures was furthermore

reflected by a statistically significant reduction of height loss compared to placebo. The anti-fracture effect was consistent over the duration of the study. There was no indication of a waning of the effect over time.
Although the clinical fracture trial for ibandronic acid was not specifically designed to demonstrate fracture efficacy in non-vertebral fractures, a relative risk reduction of similar magnitude (69%) as demonstrated for vertebral fractures was observed for non-vertebral fractures in a subgroup of patients being at higher fracture risk (femoral neck BMD T–score <–3.0 SD). The observation of non-vertebral fracture efficacy in high-risk subgroups is consistent with clinical trial findings for other bisphosphonates.
Three-year lumbar spine BMD increase compared to placebo was 5.3% for the daily regimen. Compared to baseline this increase was 6.5%.

Biochemical markers of bone turnover (such as urinary CTX and serum osteocalcin) showed the expected pattern of suppression to premenopausal levels and reached maximum suppression within a period of 3-6 months. A clinically meaningful reduction of 50% and 78 % of biochemical markers of bone resorption was observed as early as one month after start of treatment with Bonviva 2.5 mg daily and 20 mg intermittently, respectively. Decreases in biochemical markers of bone resorption were evident within 7 days of starting treatment.

Bonviva 150 mg once monthly

Bone mineral density

Bonviva 150 mg once monthly was shown to be at least as effective as Bonviva 2.5 mg daily at increasing BMD in a two-year, double-blind, multicentre study (BM16549) of postmenopausal women with osteoporosis (lumbar spine BMD T-score

below -2.5 SD at baseline). This was demonstrated in both the primary analysis at one year and in the confirmatory analysis at two years endpoint (Table 3).

Table 3: Mean relative change from baseline of lumbar spine, total hip, femoral neck and trochanter BMD after one year (primary analysis) and two years of treatment (Per-Protocol Population) in study BM16549

	One-year data in study BM16549		Two-year data in study BM16549	
Mean relative changes from baseline % [95% CI]	**Bonviva 2.5 mg daily (N=318)**	**Bonviva 150 mg once monthly (N=320)**	**Bonviva 2.5 mg daily (N=294)**	**Bonviva 150 mg once monthly (N=291)**
Lumbar spine L2-L4 BMD	3.9 [3.4, 4.3]	4.9 [4.4, 5.3]	5.0 [4.4, 5.5]	6.6 [6.0, 7.1]
Total hip BMD	2.0 [1.7, 2.3]	3.1 [2.8, 3.4]	2.5 [2.1, 2.9]	4.2 [3.8, 4.5]
Femoral neck BMD	1.7 [1.3, 2.1]	2.2 [1.9, 2.6]	1.9 [1.4, 2.4]	3.1 [2.7, 3.6]
Trochanter BMD	3.2 [2.8, 3.7]	4.6 [4.2, 5.1]	4.0 [3.5, 4.5]	6.2 [5.7, 6.7]

Furthermore, Bonviva 150 mg once monthly was proven superior to Bonviva 2.5 mg daily for increases in lumbar spine BMD in a prospectively planned analysis at one year, p=0.002, and at two years, p<0.001.
At one year (primary analysis), 91.3 % (p=0.005) of patients receiving Bonviva 150 mg once monthly had a lumbar spine BMD increase above or equal to baseline (BMD responders), compared with 84.0 % of patients receiving Bonviva 2.5 mg daily. At two years, 93.5 % (p=0.004) and 86.4 % of patients receiving Bonviva 150 mg once monthly or Bonviva 2.5 mg daily, respectively, were responders.
For total hip BMD, 90.0 % (p<0.001) of patients receiving Bonviva 150 mg once monthly and 76.7 % of patients receiving Bonviva 2.5 mg daily had total hip BMD increases above or equal to baseline at one year. At two years, 93.4 % (p<0.001) of patients receiving Bonviva 150 mg once monthly and 78.4 % of patients receiving Bonviva 2.5 mg daily had total hip BMD increases above or equal to baseline.

When a more stringent criterion is considered, which combines both lumbar spine and total hip BMD, 83.9 % ($p<0.001$) and 65.7 % of patients receiving Bonviva 150 mg once monthly or Bonviva 2.5 mg daily, respectively, were responders at one year. At two years, 87.1 % ($p<0.001$) and 70.5% of patients met this criterion in the 150 mg monthly and 2.5 mg daily arms respectively.

Biochemical markers of bone turnover
Clinically meaningful reductions in serum CTX levels were observed at all time points measured, i.e. months 3, 6, 12 and 24. After one year (primary analysis) the median relative change from baseline was -76 % for Bonviva 150 mg once monthly and -67 % for Bonviva 2.5 mg daily. At two years the median relative change was -68 % and -62 %, in the 150 mg monthly and 2.5 mg daily arms respectively.

At one year, 83.5 % (p= 0.006) of patients receiving Bonviva 150 mg once monthly and 73.9 % of patients receiving Bonviva 2.5 mg daily were identified as responders (defined as a decrease ≥50 % from baseline). At two years 78.7 % (p=0.002) and 65.6 % of patients were identified as responders in the 150 mg monthly and 2.5 mg daily arms respectively.
Based on the results of study BM16549, Bonviva 150 mg once monthly is expected to be at least as effective in preventing fractures as Bonviva 2.5 mg daily.

3.2 Pharmacokinetic Properties

The pharmacological effects of ibandronic acid are not directly related to actual plasma concentrations. This was demonstrated by various studies in animals and in humans, in which equivalent efficacy of ibandronic acid was demonstrated following either daily or intermittent regimens, consisting of a drug-free

interval of several weeks (at least 6 weeks in rats, at least 11 weeks in dogs, at least 30 days in monkeys, and at least 9.5 weeks in humans) provided the same total dose was administered over this period.

3.2.1 Absorption

The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration and plasma concentrations increase in a dose-proportional manner up to 50 mg oral intake, with greater than dose-proportional increases seen above this dose. Maximum observed plasma concentrations were reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability was about 0.6%. The extent of absorption is impaired when taken together with food or beverages (other than plain water).

Bioavailability is reduced by about 90% when ibandronic acid is administered with a standard breakfast in comparison with bioavailability seen in fasted subjects. There is no meaningful reduction in bioavailability provided ibandronic acid is taken 60 minutes before a meal. Both bioavailability and BMD gains are reduced when food or beverage are taken less than 60 minutes after Bonviva.

3.2.2 Distribution

After initial systemic exposure, ibandronic acid rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 l and the amount of dose reaching the bone is estimated to be 40-50% of the circulating dose. Protein binding in human plasma is low (approximately 85% bound at therapeutic concentrations), and thus there is a low potential for drug-drug interaction due to displacement.

3.2.3 Metabolism

There is no evidence that ibandronic acid is metabolized in animals or humans.

3.2.4 Elimination

The absorbed fraction of ibandronic acid is removed from the circulation via bone absorption (40-50%) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronic acid is eliminated unchanged in the feces.

The range of observed apparent half-lives is broad and dependent on dose and assay sensitivity, but the apparent terminal half-life is generally in the range of 10-72 hours. Early plasma levels fall quickly reaching 10% of peak values within 3 and 8 hours after intravenous or oral administration respectively.

Total clearance of ibandronic acid is low with average values in the range 84-160 ml/min. Renal clearance (about 60 ml/min in healthy postmenopausal females) accounts for 50-60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances is considered to reflect the uptake by bone.

3.2.5 Pharmacokinetics in Special Populations

Gender

Bioavailability and pharmacokinetics of ibandronic acid are similar in both men and women.

Race
There is no evidence for clinically relevant interethnic differences between Asians and Caucasians in ibandronic acid disposition. There are few data available on patients of African origin.

Patients with renal impairment
Renal clearance of ibandronic acid in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLcr).
No dosage adjustment is necessary for patients with mild or moderate renal impairment (CLcr ≥30 ml/min), as shown in study BM16549 where the majority of patients fell into these categories.

Subjects with severe renal impairment (CLcr ≤ 30 ml/min) receiving oral administration of 10 mg ibandronic acid daily for 21 days, had 2- to 3-fold higher plasma concentrations than subjects with normal renal function (total clearance = 129 ml/min). Total clearance of ibandronic acid was reduced to 44 ml/min in the subjects with severe renal impairment. After i.v. administration of 0.5 mg, total, renal, and non-renal clearances decreased by 67%, 77% and 50%, respectively, in subjects with severe renal impairment. However, there was no reduction in tolerability associated with the increase in exposure.

Patients with hepatic impairment

There are no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver has no significant role in the clearance of ibandronic acid which is not metabolized but is cleared by renal excretion

and by uptake into bone. Therefore, dosage adjustment is not necessary in patients with hepatic impairment. Further, as protein binding of ibandronic acid is low (85%) at therapeutic concentrations, hypoproteinemia in severe liver disease is unlikely to lead to clinically significant increases in free plasma concentration.

Elderly
In a multivariate analysis age was not found to be an independent factor of any of the pharmacokinetic parameters studied. As renal function decreases with age, this is the only factor to take into consideration (see chapter *Patients with renal impairment*, above).

Children
There are no data on the use of Bonviva in patients less than 18 years old.

3.3 Preclinical Safety

Toxic effects in animals were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

3.3.1 Carcinogenicity

No indication of carcinogenic potential has been observed.

3.3.2 Mutagenicity

No indication of genotoxic potential has been observed.

4. PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

Tablet core

Lactose monohydrate	Ph. Eur./NF
Povidone	Ph. Eur./USP
Cellulose, microcrystalline	Ph. Eur./NF
Crospovidone	Ph. Eur./NF
Stearic acid, purified	Ph. Eur./NF
Silica, colloidal anhydrous	Ph. Eur./NF

Tablet coat

Hypromellose	Ph. Eur./USP
Titanium dioxide	Ph. Eur./USP
Talc	Ph. Eur./USP
Macrogol, 6,000	Ph. Eur./NF

4.2 Storage

Do not store above 30°C.

4.3 Special Instructions for Use, Handling and Disposal

This medicine should not be used after the expiry date (EXP) shown on the pack.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available in your location.

4.4 Packs

Film-coated tablets 150 mg 1, 3

Medicine: keep out of reach of children

Current at December 2015

Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel

10174522 FE

Genisys-No.	10174522 FE
Printing Colour:	Pantone 281/Pantone 271
Format:	108x42 mm NP 9376
Folding Format:	plano
Type Size	7 pt
Drawing Norm	29.09.09

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